



Long- and short-range connectivity and neuronal types affect prefrontal dorsal raphe circuit dynamics differently

Joshi, A., Rhodes, O., Sharp, T., Furber, S., & Wong-Lin, K. (2020). *Long- and short-range connectivity and neuronal types affect prefrontal dorsal raphe circuit dynamics differently*. Abstract from Neuromatch.

[Link to publication record in Ulster University Research Portal](#)

Publication Status:

Published (in print/issue): 30/03/2020

Document Version

Publisher's PDF, also known as Version of record

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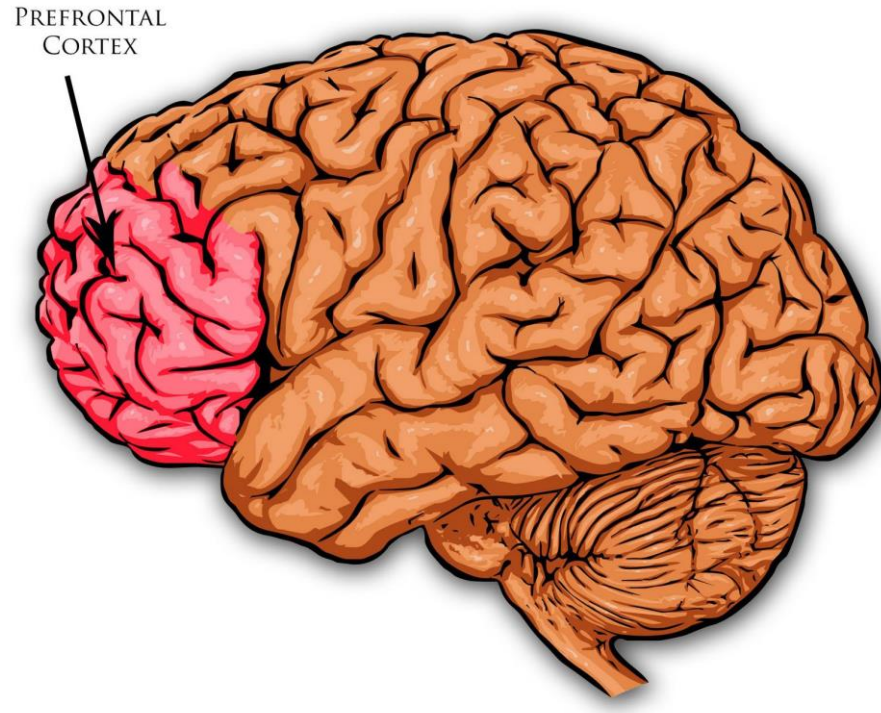
Long- and short-range connectivity and neuronal types affect prefrontal dorsal raphe circuit dynamics differently

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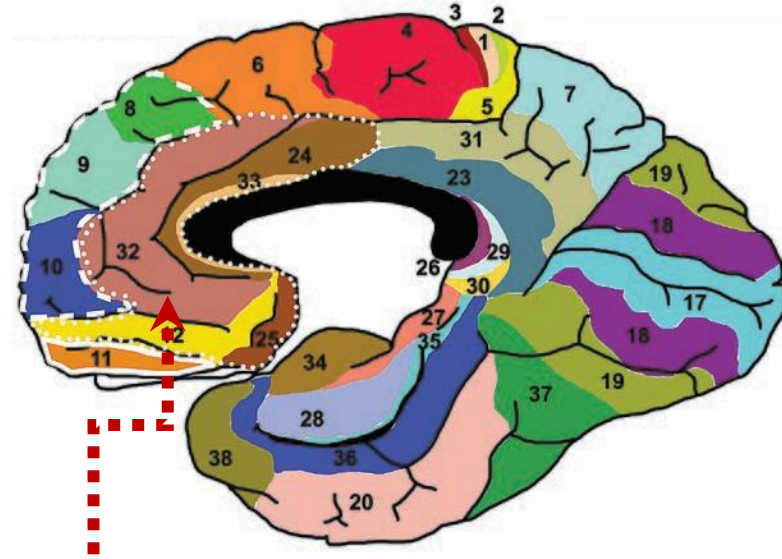
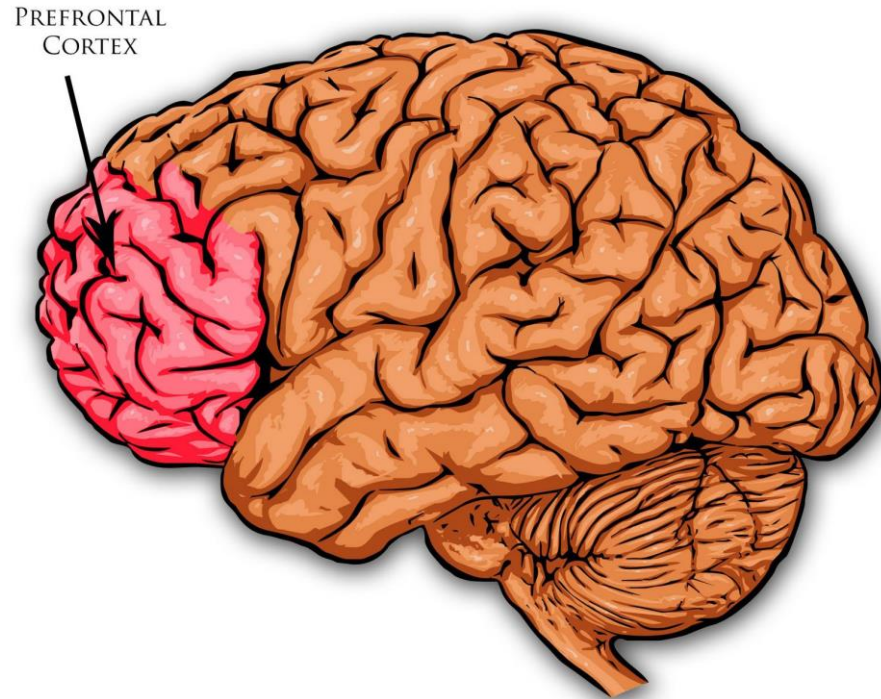


Prefrontal cortex



Prefrontal cortex (PFC) plays a key role in high-level cognitive functions such as attention, memory, decision-making, and mood regulation.

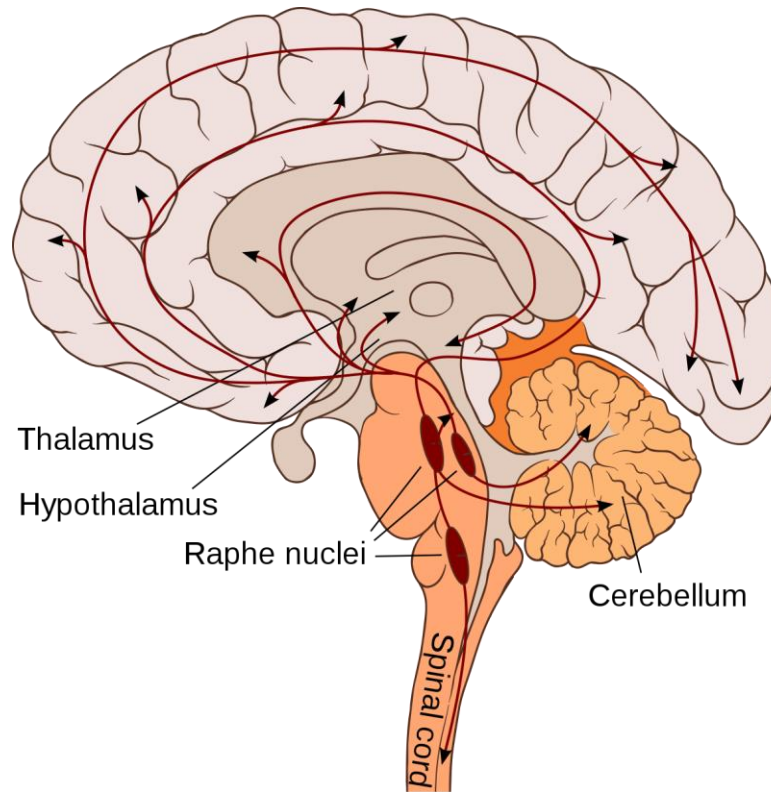
Prefrontal cortex



***Medial prefrontal cortex (mPFC):
Brodmann areas 12, 24, 25, 32, 33***

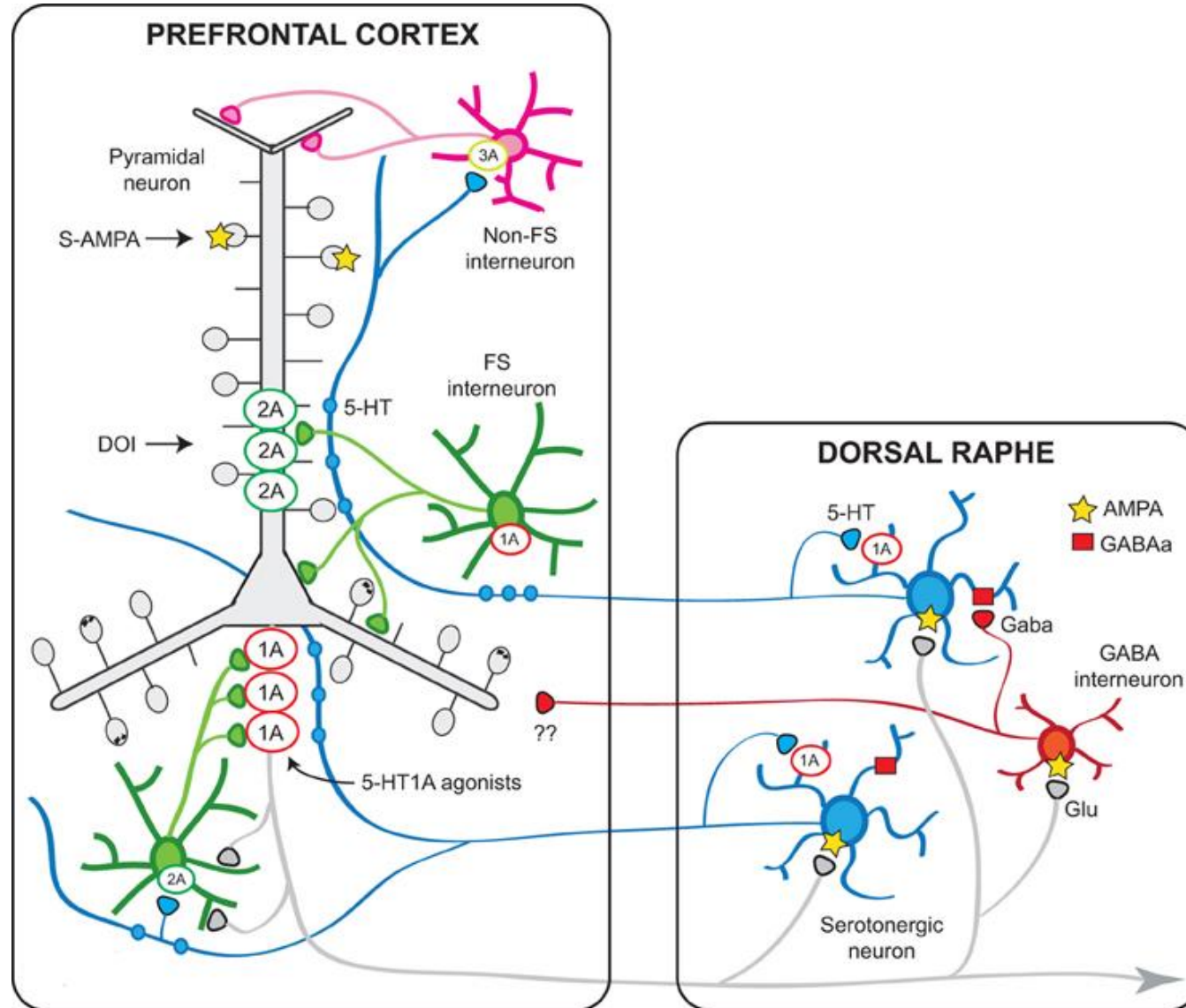
Prefrontal cortex (PFC) plays a key role in high-level cognitive functions such as attention, memory, decision-making, and mood regulation.

Dorsal raphe nucleus (DRN)



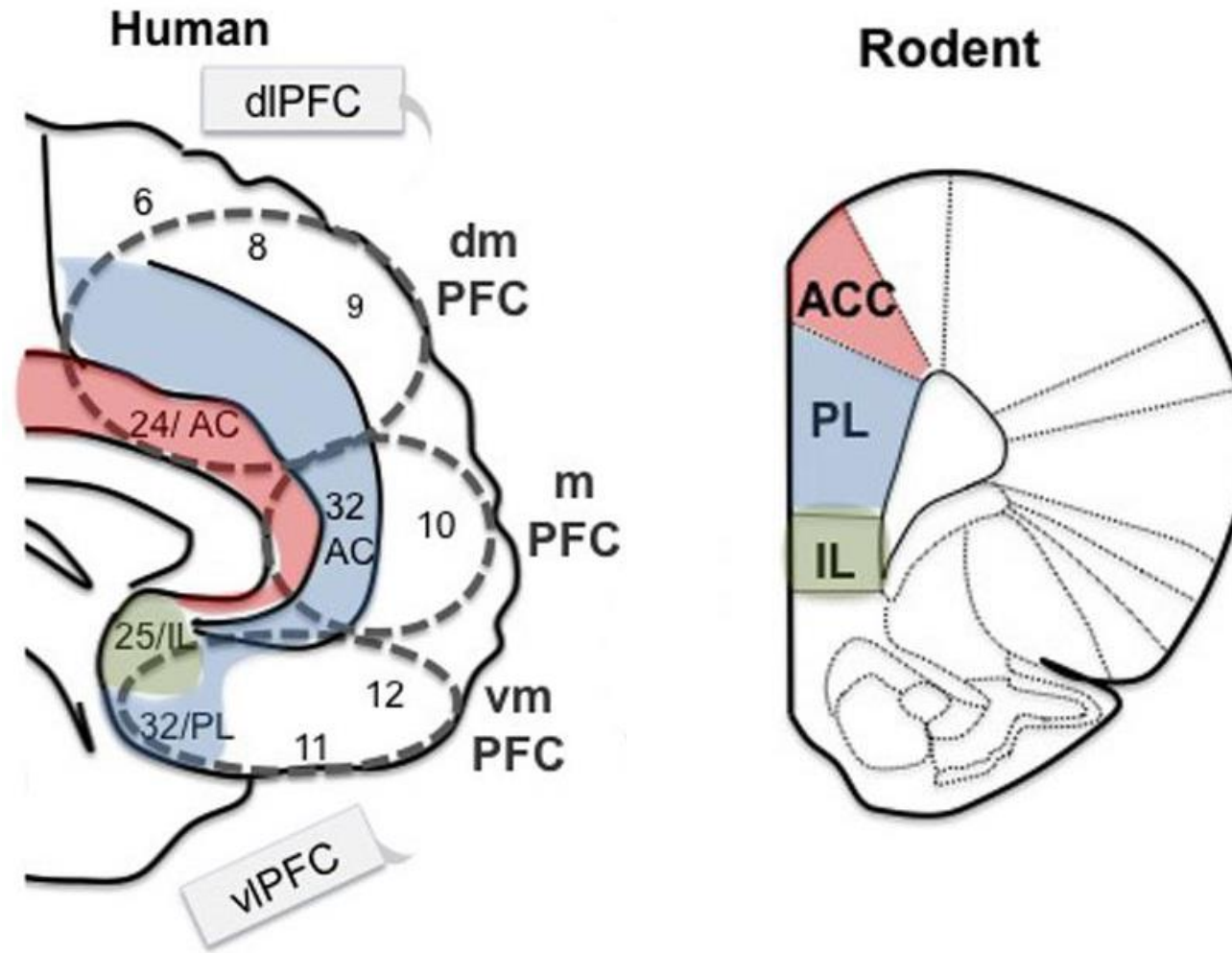
- PFC receives dense serotonergic (5-HT) innervation from DRN.
- DRN is located in the midbrain and pons.

PFC-DRN interaction (closed loop)



(Celada, Puig and Artigas 2013)

Medial prefrontal cortex- Prelimbic cortex (PL)

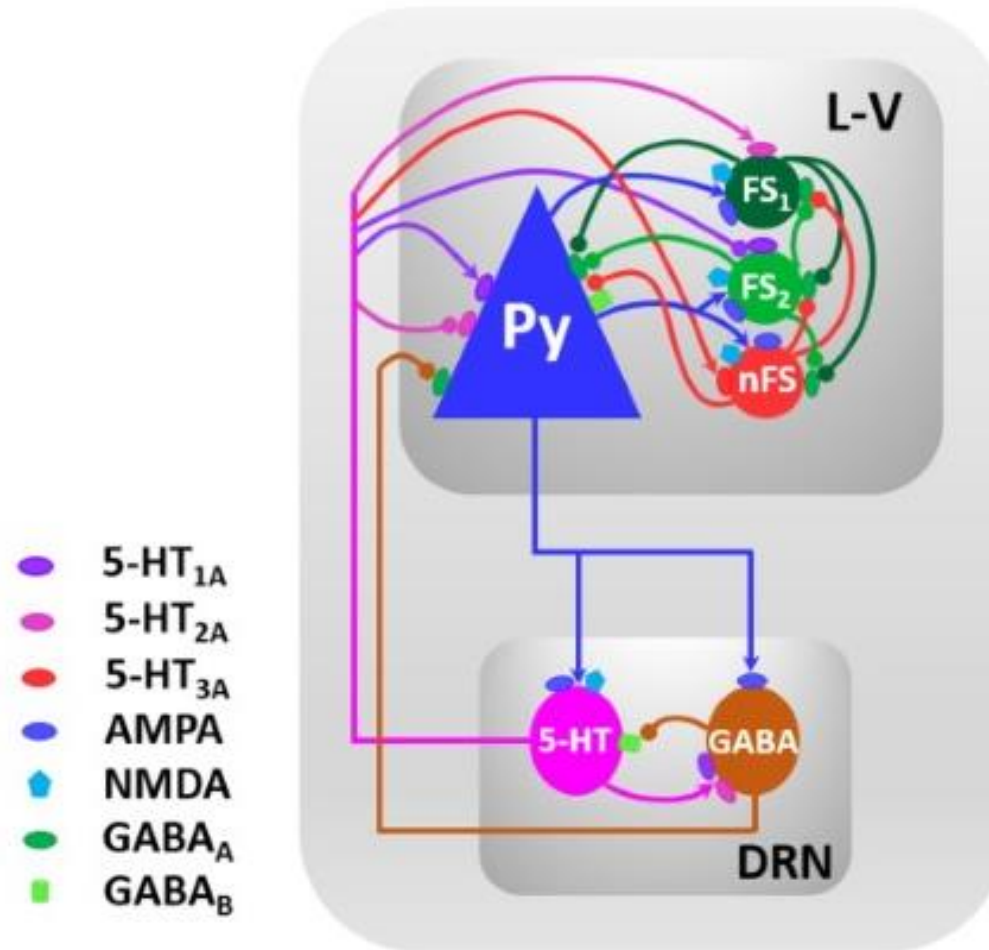


Bicks et al., 2015

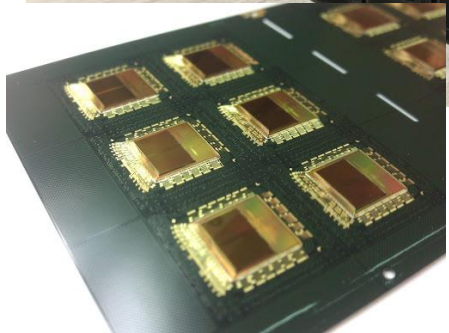
Research Questions

- What is the collective dynamics of PFC-DRN interaction? With the focus on PL-DRN system?
- How the long- and short-range connections in PL-DRN contribute to its collective dynamics?
- What is the role of PL and DRN neuronal types?

PL-DRN interaction

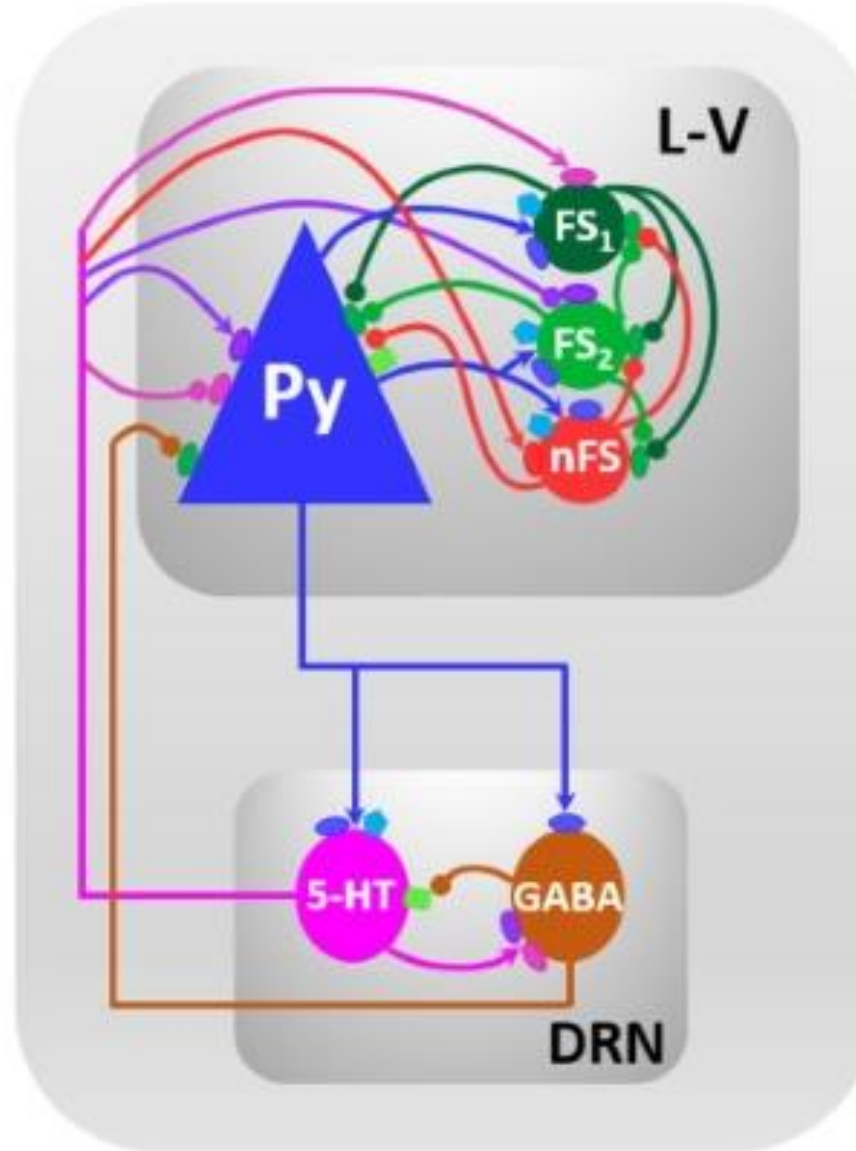


PL-DRN interaction



SpiNNaker
(University of
Manchester)

- 5-HT_{1A}
- 5-HT_{2A}
- 5-HT_{3A}
- AMPA
- NMDA
- GABA_A
- GABA_B



L-V

of Py neurons ~ 6300

of FS1/FS2 neurons ~389

of nFS neurons ~81

DRN

of 5-HT neurons ~ 13250

of GABA neurons ~ 6625

Computational model

Single neuron model: Izhikevich type model:

$$\frac{dV}{dt} = 0.04V^2 + 5V + 140 - U + I_{DC,i} + I_{Background,i} + I_{Syn,i}$$

$$\frac{dU}{dt} = a(bV - U) \quad \text{If } V \geq V_{Peak}, \text{ then } V = c \text{ and } U = U + d$$

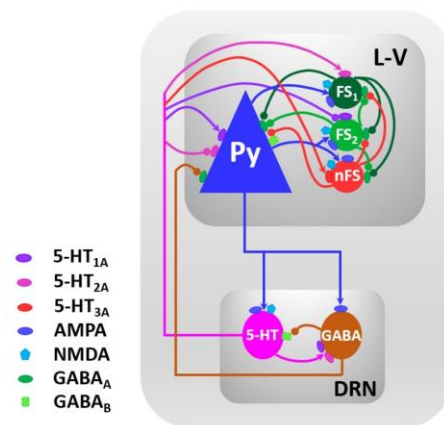
Synaptic current:

$$I_{Syn} = wf \left(e^{-t/\tau_1} - e^{-t/\tau_2} \right), w \text{ is synaptic weight, } f \text{ is scaling factor}$$

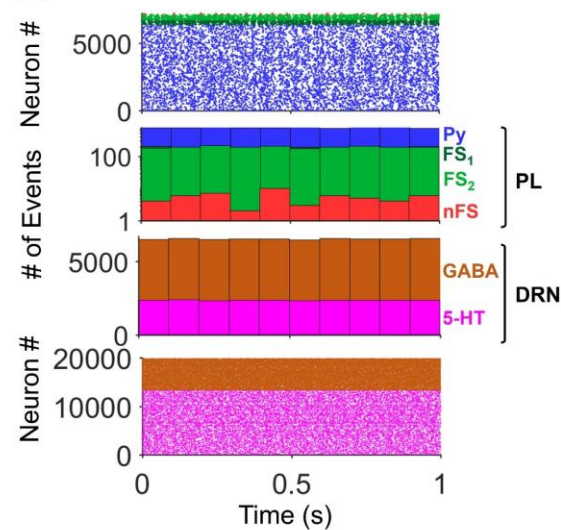
τ_1, τ_2 are time constants estimated from experiments for different synapses

*Baseline PL-DRN
neural activities
with multiple
network
frequency bands
can co-exist.*

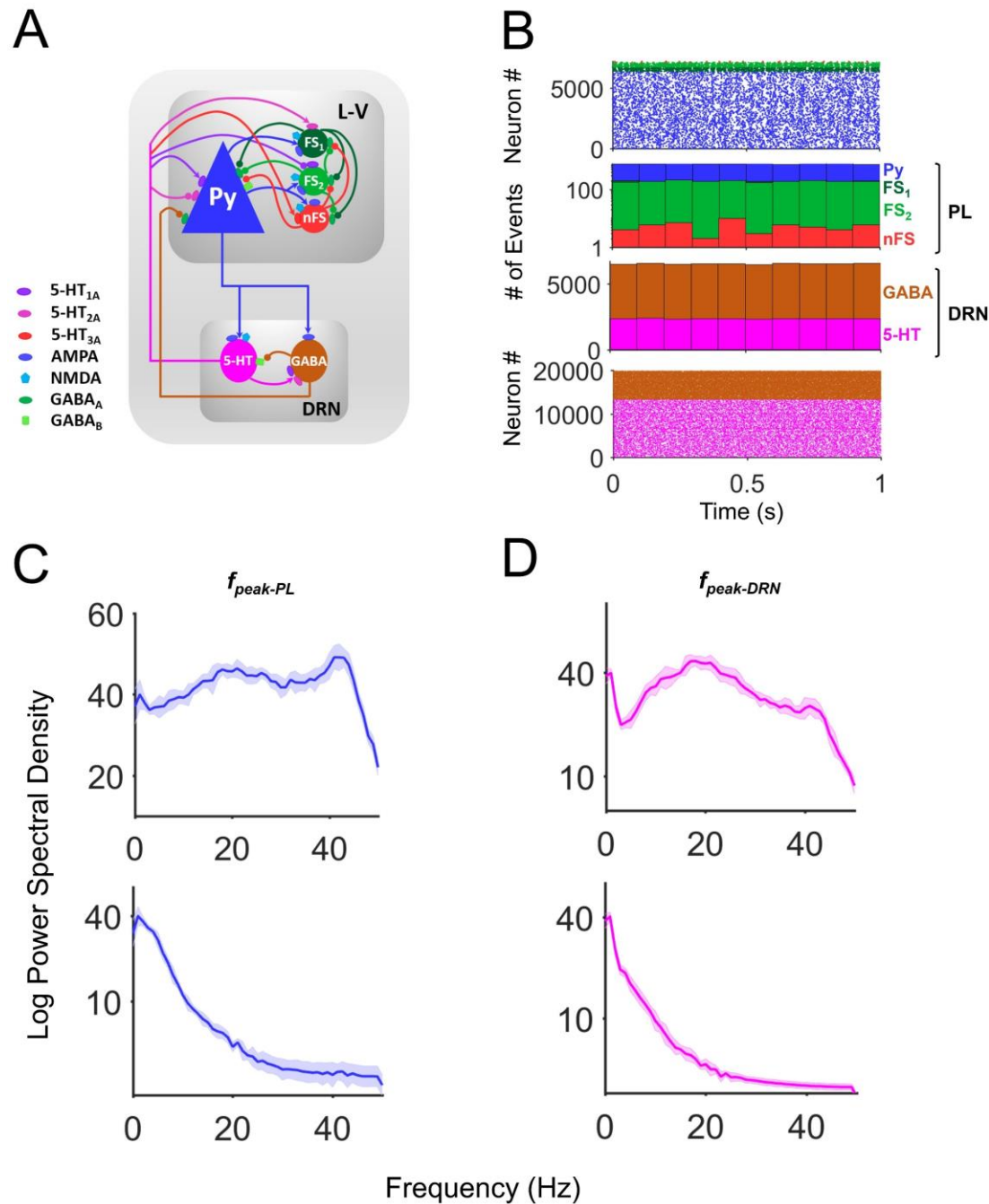
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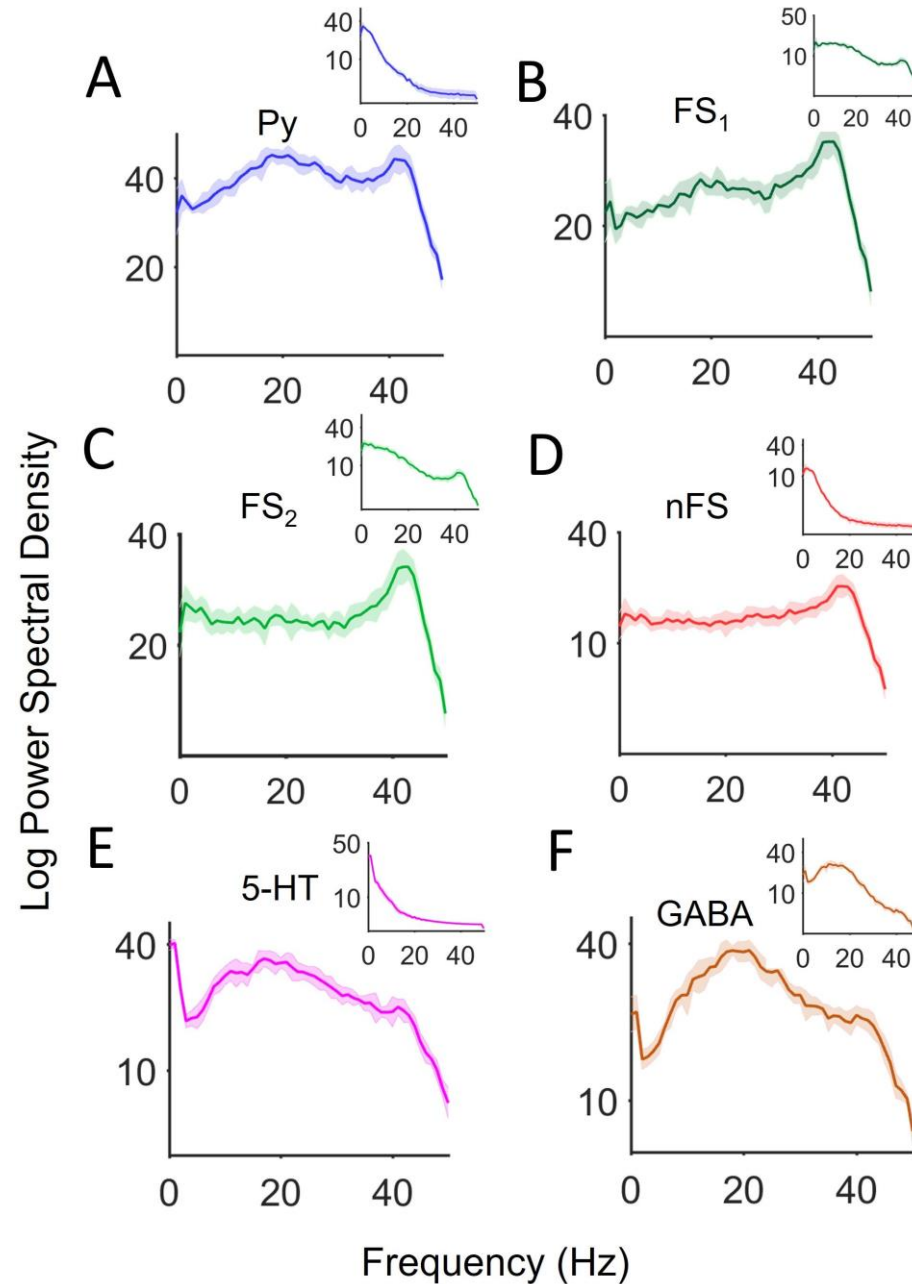
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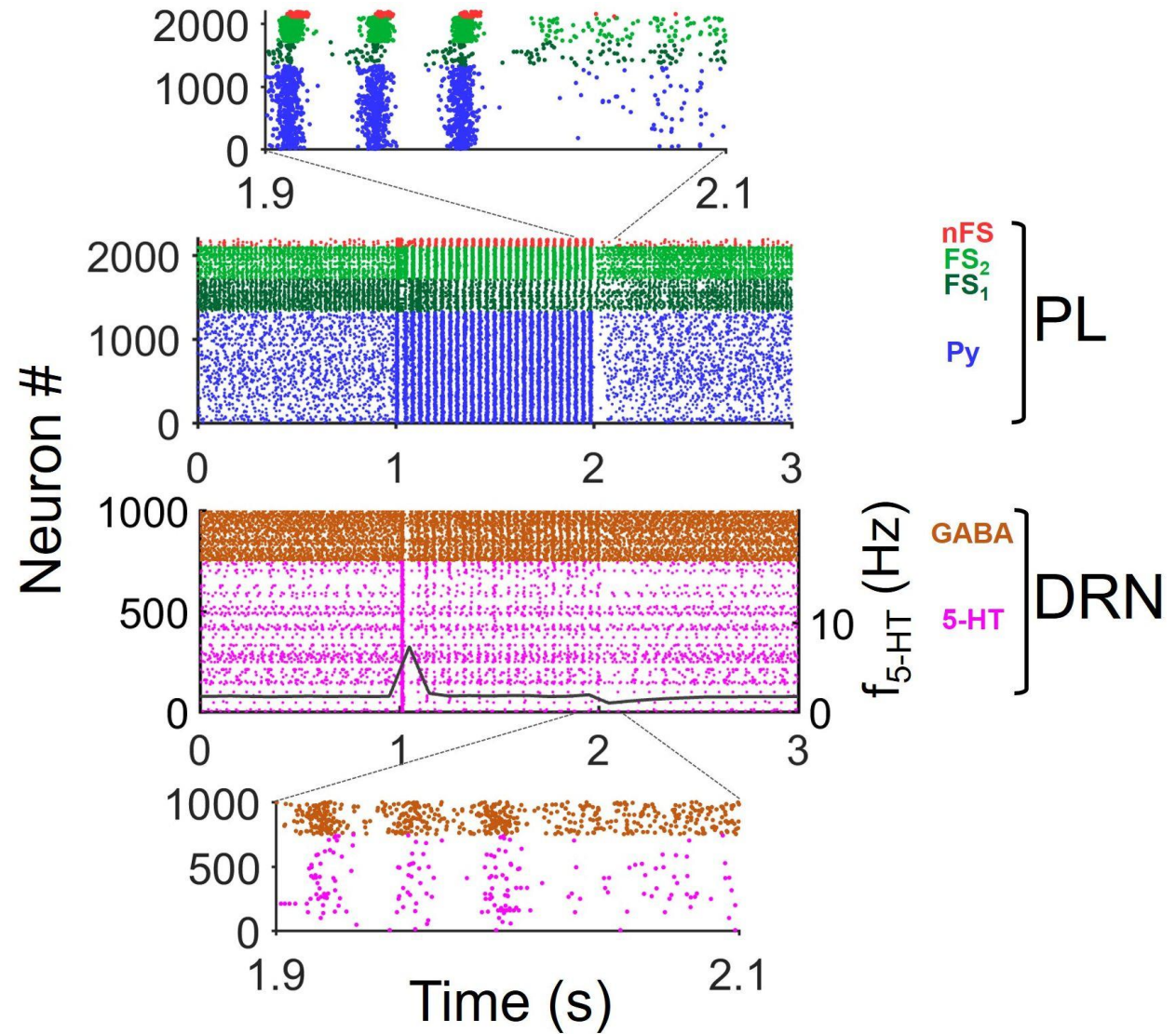
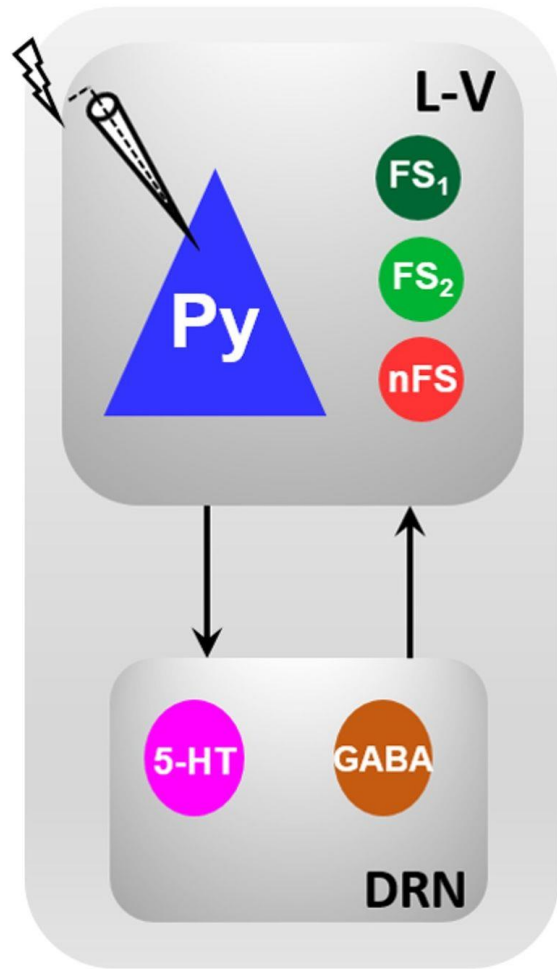
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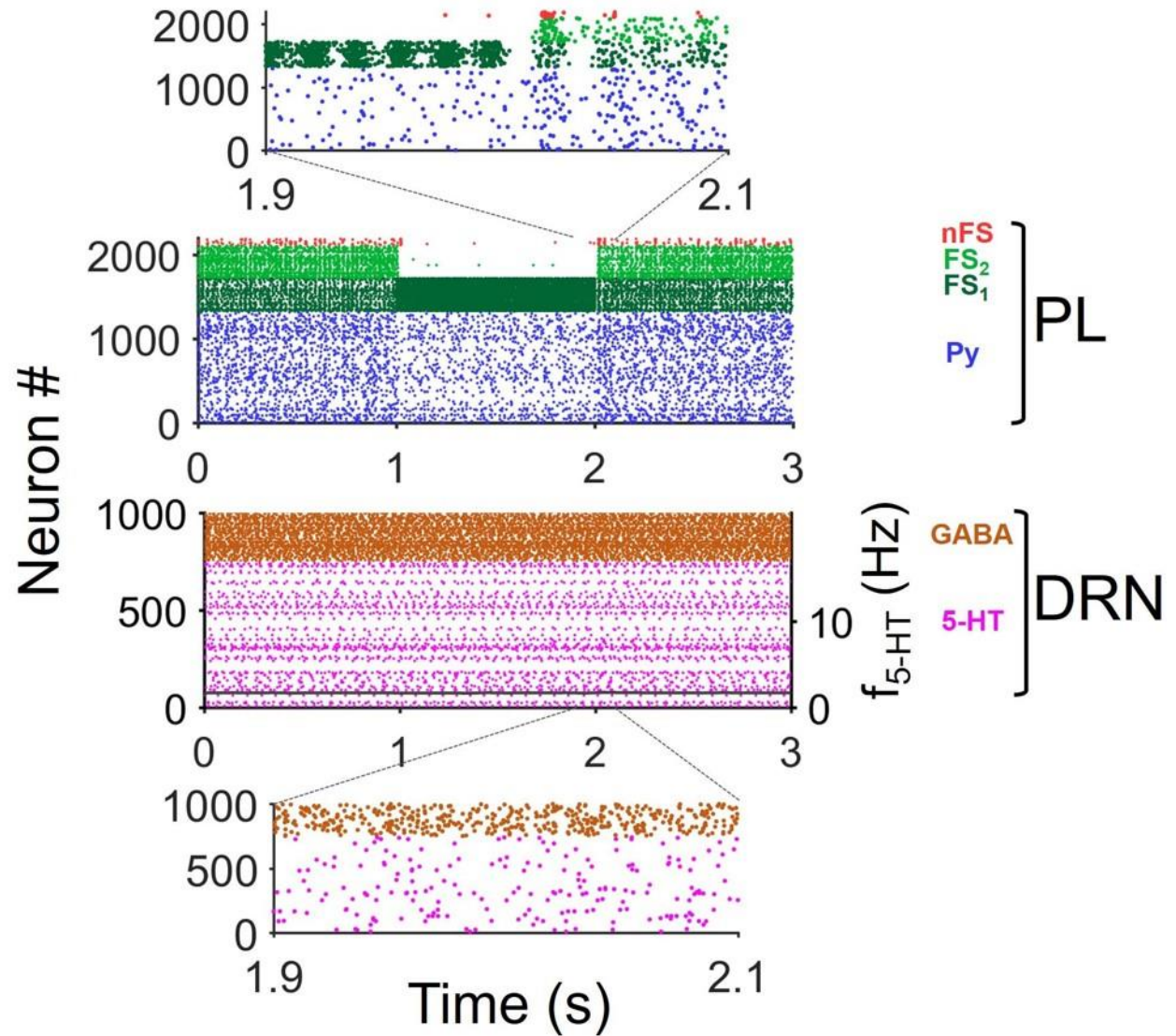
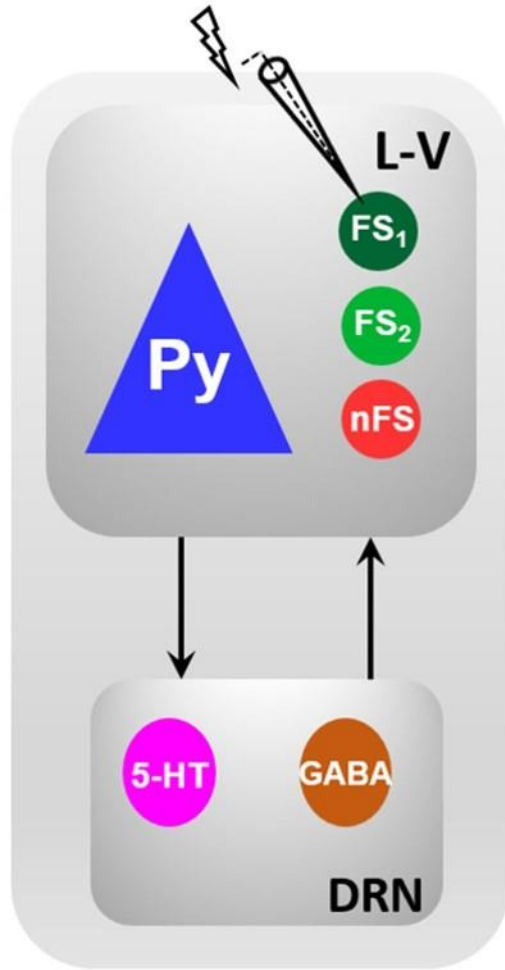
*Multiple network
frequency bands
co-exist for
distinct neuronal
populations*



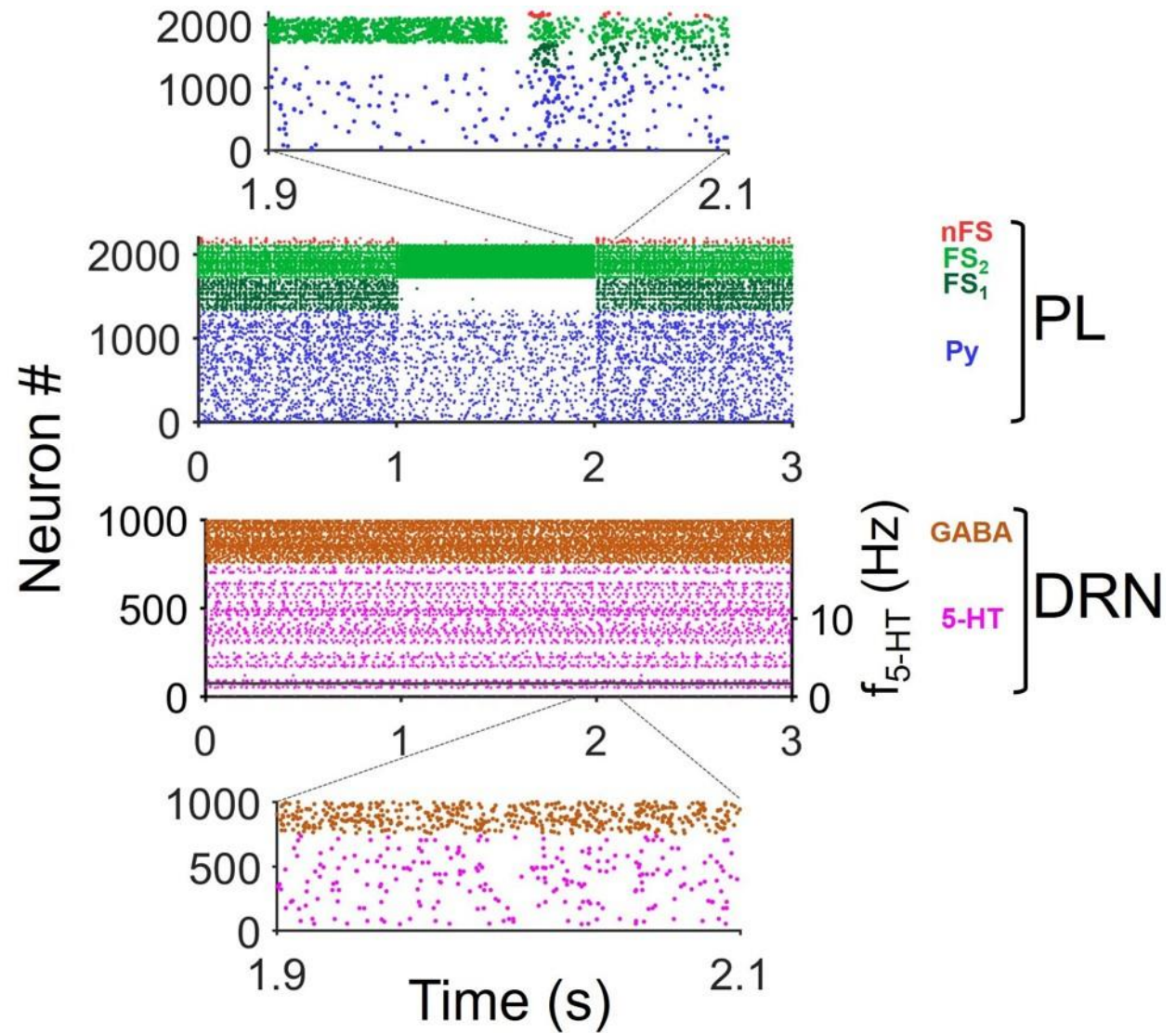
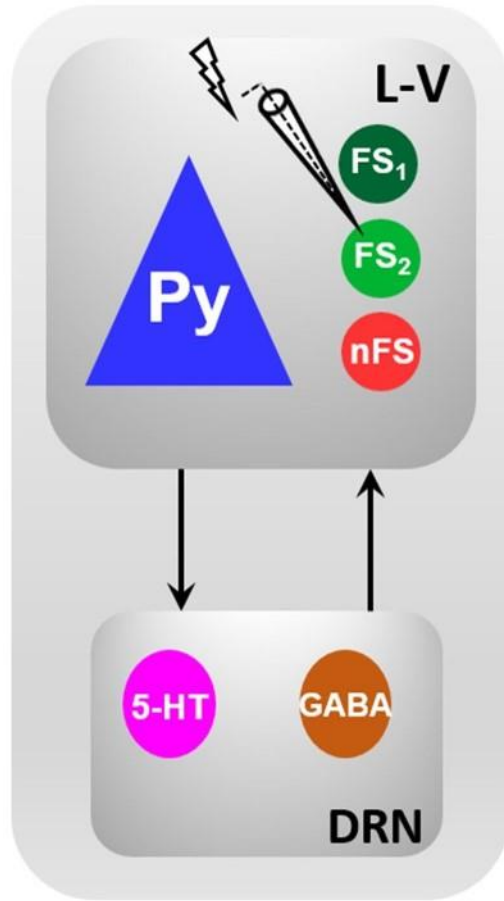
Stimulation of PL pyramidal neurons transiently activates DRN 5-HT and GABAergic neurons



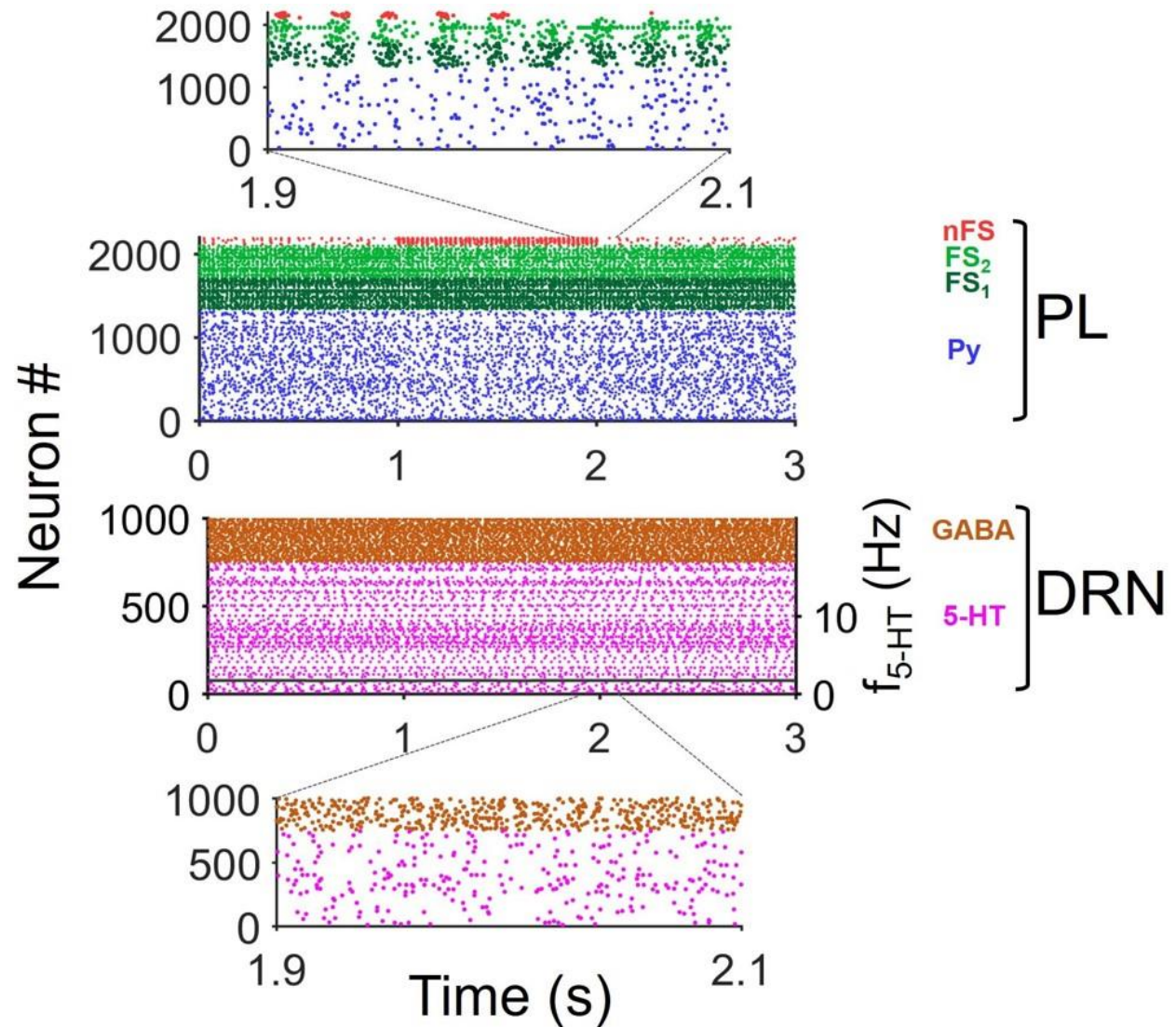
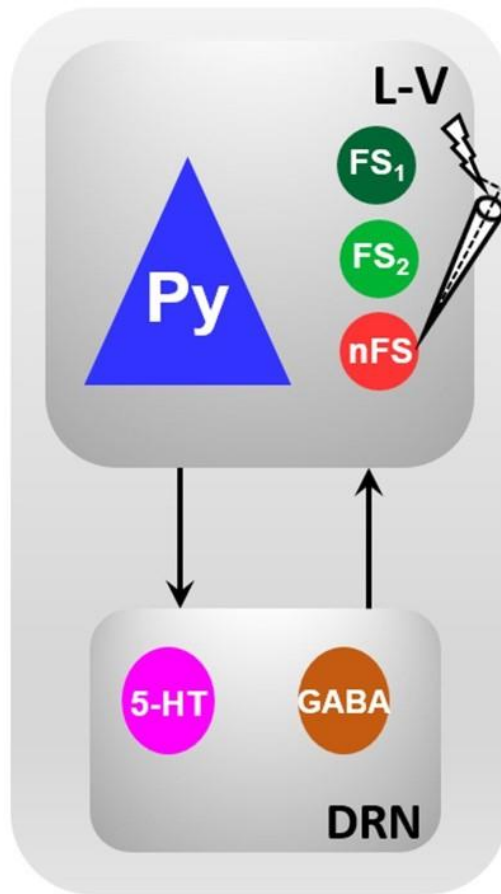
Stimulation of PL interneurons have negligible impact on DRN 5-HT and GABAergic neurons



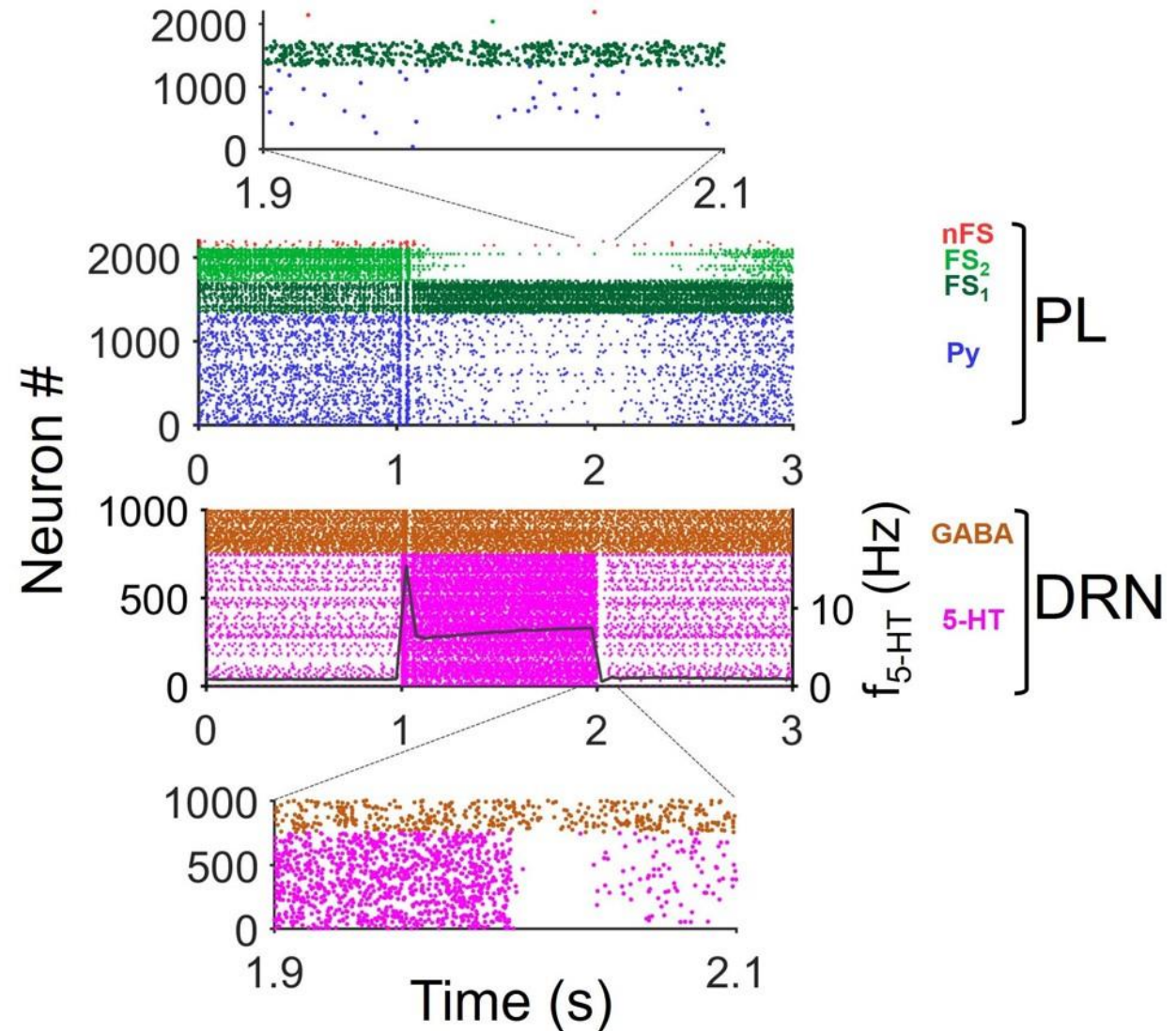
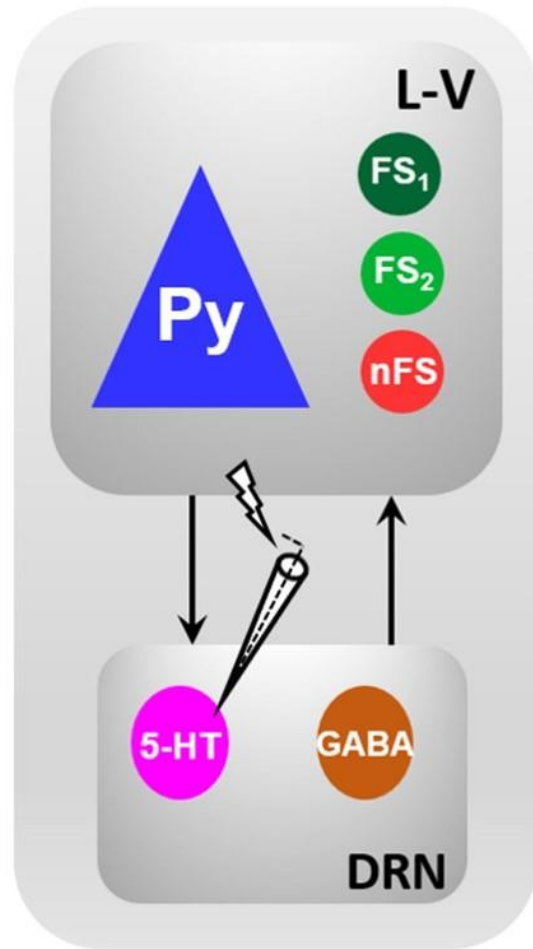
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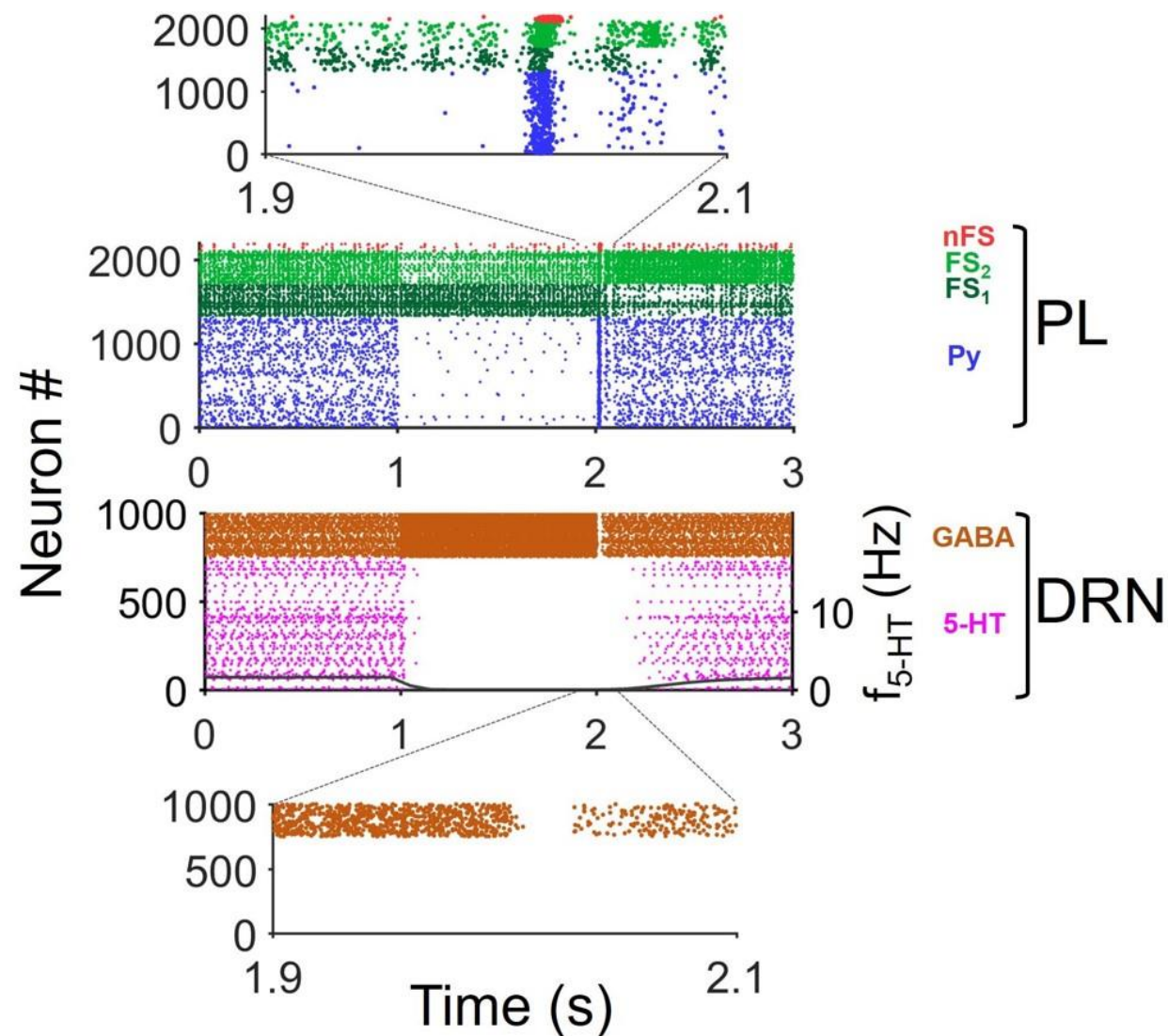
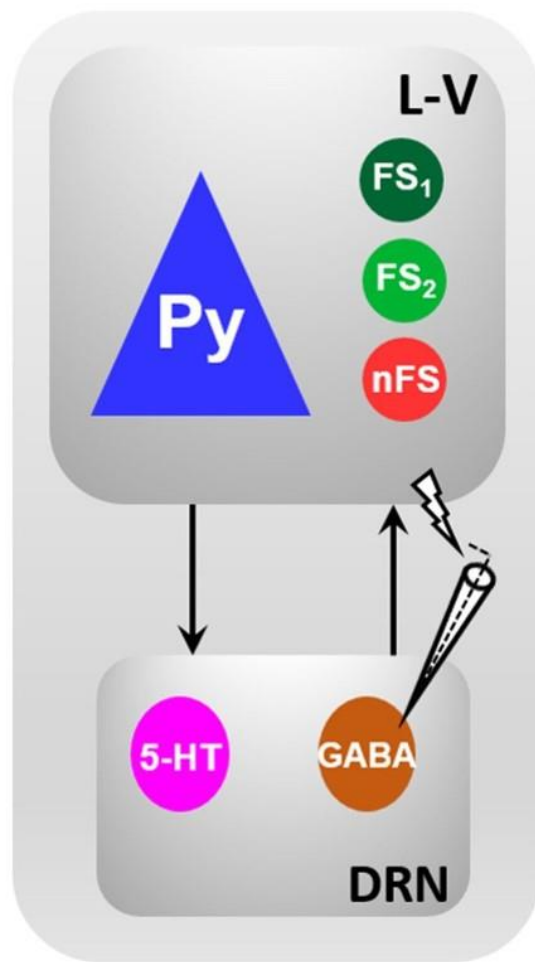
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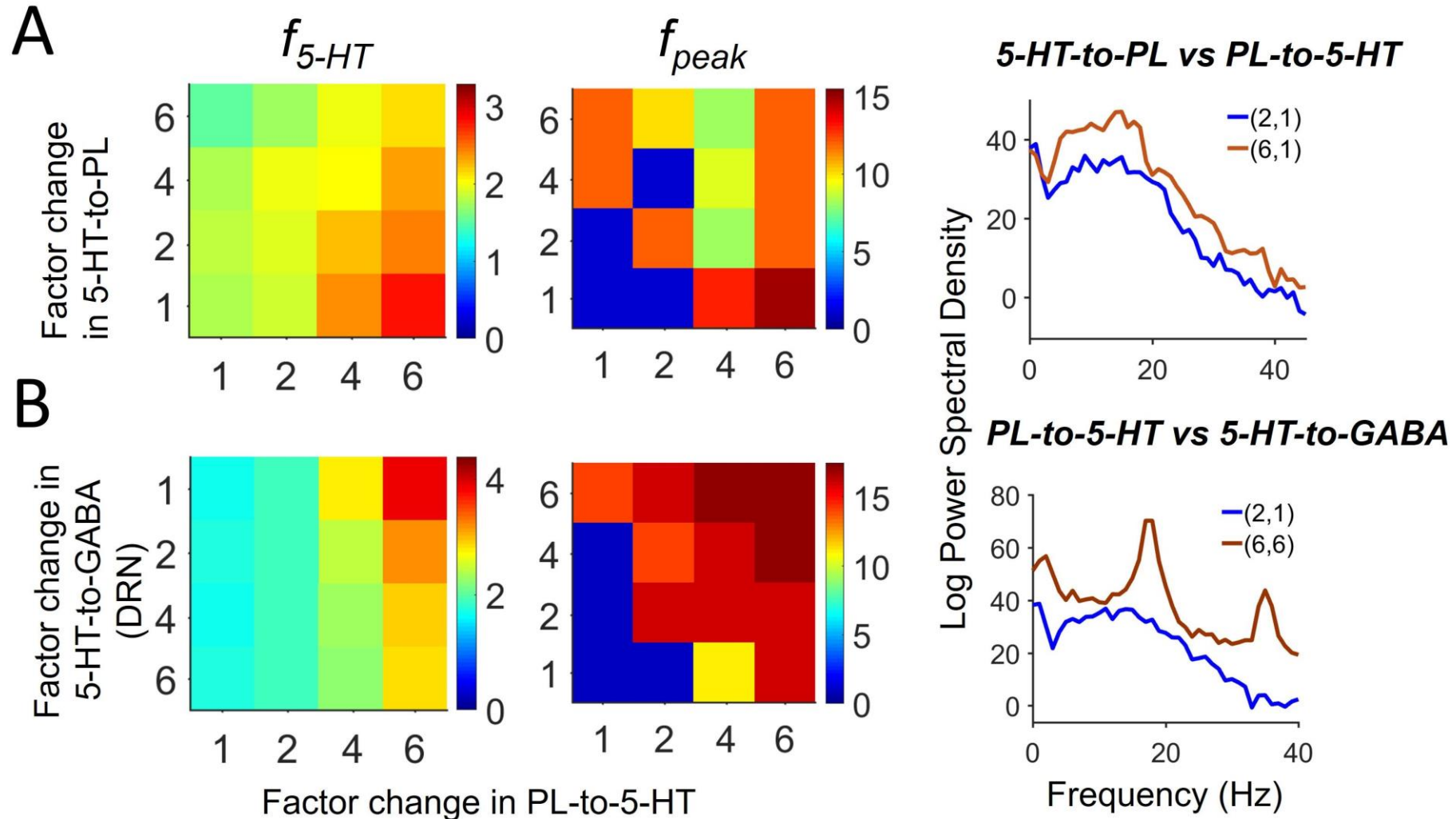
5-HT stimulation activates 5-HT neurons and inhibits Py neurons



GABAergic stimulation is stronger than 5-HT and inhibits significant Py and 5-HT neurons



Stronger long-range PL-to-5-HT or local short-range 5-HT-to-GABA connections, enhances higher DRN frequency oscillations



Conclusion

- Developed the first closed-loop model of the PFC-DRN, focusing on PL.
- Model supports co-existence of baseline firing activities and multiple network frequency bands observed in various separate experimental studies.
- Stimulation of PL pyramidal, but not PL GABAergic, neurons transiently activates DRN 5-HT and GABAergic neurons.
- Stronger long-range PL-to-5-HT or local short-range 5-HT-to-GABA connections, enhances higher DRN frequency oscillations, primarily mediated by DRN GABAergic neurons.
- Computational model lays the foundation towards developing more realistic closed-loop neuronal circuits for systematic understanding of chemical neuromodulation and its links to cognition and brain disorders.

Acknowledgements

Ulster University

- *KongFatt Wong-Lin*

University of Oxford

- *Trevor Sharp*

University of Manchester

- *Oliver Rhodes*
- *Steve Furber*
- *Andrew Rowley*
- *Michael Hopkins*
- *Alan Stokes*

